REMARKS

Claims 1-4, 6-15, and 17-63 were pending in the subject application. Claims 11-63 were withdrawn from consideration by the Examiner as directed to nonelected subject matter. By the amendment, Claims 2, 3, 4, 6, 8, 11-15 and 17-63 have been canceled without prejudice or disclaimer, and Claims 1, 7, 9 and 10 have been amended. Applicant maintains that the claim amendments do not raise an issue of new matter. Support for the claim amendments can be found in at least Claims 2, 3, 4 and 8. Entry of the amendments is respectfully requested.

Provisional Obviousness-type Double Patenting Rejections

Applicant acknowledges the provisional rejection of Claims 1-4 and 6-9 as being unpatentable over Claims 1-4 and 42 of co-pending U.S. Patent Application 10/984,683 and over Claims 82-84 and 100-101 of co-pending U.S. Patent Application 10/580,962.

Rejections under 35 U.S.C. §112 First Paragraph

Claims 1-4 and 6-10 are rejected as failing to comply with the written description and enablement requirements of 35 U.S.C. §112, first paragraph. Re-consideration and withdrawal of this rejection are requested in view of the amendments made herein above.

Rejections under 35 U.S.C. §103(a)

Claims 1-4 and 6-10 are rejected as being unpatentable over Dudley et al. (US2004/0002482) in view of Dodman (U.S. 5,762,960) and further in view of Sanchez (US2002/0086899).

Applicant respectfully traverses this rejection.

Applicant directs the Examiner's attention to the following.

Anxiety disorders - the present invention. Psychological as well as somatic symptoms

of anxiety are frequently observed phenomena of depression ("anxiety symptoms"). These symptoms are a subsidiary effect and specifically linked to a depression. As a corollary, said symptoms will disappear upon amelioration of the depression. As such, the Examiner may be deemed correct that "psychological anxiety is a psychological aspect of depression" (see Dudley et al., below).

However, ***primary anxiety disorders*** also exist ("anxiety disorder"; cf. DSM IV). These anxiety disorders are a disorder as such, i.e. they are ***not*** related to other disorders such as depression. Obsessive Compulsive Disorder (OCD) is the most widely known anxiety disorder. Indeed, this anxiety disorder is wholly unrelated to depression. (Nevertheless, an anxiety disorder can be accompanied by a secondary depression. In particular, a patient may become depressed because of his/her awareness of being obsessed and/or compulsive).

Hence, although superfluously it may seem that "anxiety symptoms" and "anxiety disorder" are related, they have a different, entirely unrelated underlying cause.

It is long since known that SSRIs are effective in treating anxiety disorders (independent of whether this anxiety disorder is accompanied by a depression or not). Hence, the SSRIs have at least a two fold effect as an anti-depression drug and as an anti-anxiety drug. Notably, the efficacy in anxiety disorders is directed towards treating this anxiety disorder as such, but is completely unrelated to treating a depression. This can be observed in patients having e.g. OCD but not a secondary depression.

In the present invention, a low dose pipamperone when administered in combination with an SSRI enhances the efficacy of the SSRI in ***anxiety disorders***.

In this regard, it is well-known that pipamperone at the ubiquitously used (high) prior art doses indeed decreases the symptom of psychological anxiety (see e.g. information by manufacturer attached hereto). This effect of pipamperone results from a neuroleptic-sedative effect. Specifically, it is known that the high dose pipamperone

results in D2 receptor-related dopaminergic and H1 receptor-related histaminergic antagonism, which is responsible for the neuroleptic-sedative effect. This antagonizing effect (resulting in this neuroleptic-sedative effect) is absent at the claimed low dose of 5-15 mg/day. Accordingly, there would be no incentive to decrease the amount of pipamperone administered, since this would lower the neuroleptic-sedative effect (see also below). Moreover, there is no incentive to use pipamperone for anxiety disorders.

The cited art has to be interpreted in the context referred to above.

Dudley et al.

The Examiner asserts that Dudley et al. (on page 59, paragraph 523) mentions that psychological anxiety is a psychological aspect of depression.

Dudley et al. relates to testosterone. Dudley et al. aims at and relates to treating a depressive disorder (mood disorder) by administering percutaneously compositions and combinations comprising a steroid in the testosterone synthetic pathway in subjects ***failing*** to respond to conventional antidepressants and/or who exhibited low or borderline testosterone levels. Indeed, the use of testosterone pervades throughout the detailed description. The use of testosterone as the primary compound is further explicitly confirmed in paragraphs 119 - 121, 148 - 162, the Examples in general, Examples 1 - 9 (paragraphs 246 - 492) in particular, paragraphs 472-473 relating to mood assessment in response to testosterone alone, the Figures and, first and foremost, the claims.

Dudley et al. teaches combinations with testosterone. Even if a combination of compounds is administered, then the first compound is always and invariantly testosterone or a steroid in the testosterone synthetic pathway. Indeed, paragraph 122 relates to "methods, kits, combinations and compositions" which are used ***in conjunction*** with a pharmaceutical agent, such as an antidepressant. In paragraph 124 "the present invention employs testosterone ***in conjunction*** with a pharmacologically-

effective amount of ... an anti-depressant..." (emphasis added). Paragraph 172 is exemplary in this regard stating that "[i]n another embodiment of the methods, kits, combinations and compositions of the present invention, the composition ***and*** the therapeutic agent are administered substantially simultaneously, or sequentially" (emphasis added). Hence, the therapeutic agent is ***not*** considered as part of the invention as such in Dudley et al.

Thus, when considering Dudley et al., the person skilled in the art would be taught administering at least testosterone when treating depression.

The sections referred to by the Examiner should be considered in this context. The term "methods, kits, combinations and compositions for treating ...." used in Dudley et al., always comprises testosterone and possibly a second compound. In paragraphs 131 - 133, the antidepressant agents which can be used ***in conjunction*** with testosterone are exemplified. Although it is mentioned in the last sentence that combinations can be used of the antidepressants, these combinations are to be used ***in conjunction*** with testosterone.

Indeed, Example 11 (paragraphs 494-506) relates to treating erectile dysfunctions using testosterone and a hypothetical phosphodiesterase inhibitor (phosphodiesterase inhibitors are not SSRIs). In Example 12 (paragraphs 507 - 523), which relates to method of treating a subject suffering from a depressive disorder, the subjects were treated with testosterone, and taking an adequate dose of antidepressant medication, but still complaining of depressive symptoms (paragraph 508).

Thus, Dudley et al. teaches administering at least testosterone. As a corollary, the antidepressant is ***not*** considered as part of the invention as such.

Finding the combination citalopram - pipamperone amounts to undue burden. In paragraph 132, over 140 antidepressants are listed. Each and every combination would encompass about 10^{158} possibilities. Even if only a combination of only two compounds is

contemplated, about 10,000 possibilities are disclosed. Moreover, Dudley et al. list the preferred antidepressant agents in paragraph 133, which do not include pipamperone or citalopram.

Hence, applicant maintains that Dudley et al. does not teach or suggest the combination of pipamperone and citalopram to treat an anxiety disorder. Moreover, it would be undue burden to test each and every combination in order to come to pipamperone and citalopram (of course from Dudley et al. to used in conjunction with testosterone).

Only the amount of testosterone is provided. Applicant respectfully maintains that the reference by the Examiner to paragraphs 158 - 172 regarding the amount of doses is interpreted erroneously. Specifically, the preceding paragraphs 140 - 157 relate exclusively to the amount of testosterone, but not to the amount of the antidepressant. Indeed, paragraphs 158 - 162 do not refer to an antidepressant, even less to the amount thereof. Only in paragraph 169, Dudley et al. contemplates a combination of testosterone with an antidepressant, but again without providing or suggesting the amount of the antidepressant. Paragraph 170 refers to 10 μg steroid, but neither this section, nor paragraphs 171 or 172 refer to any amount of the antidepressant. Again, when discussing the invention, the amounts of steroid, the penetrating agent, the thickening agent and the lower alcohol are given, but not the amount of the antidepressant (see paragraphs 174-179). Thus, no explicit amount or range of amounts is provided for the antidepressant in Dudley et al., and even less for pipamperone.

Determining the amount of an antidepressant is not routine. Dudley et al. mentions in paragraph 180 that "[t]he amount of the testosterone and the amount of the therapeutic agent together make a depressive-disorder effective amount."

A depressive-disorder effective amount is further described in paragraph 188, which notes that the concentration of the therapeutic agent is such that a therapeutic

level of agent is delivered over the term that the composition is to be used. The amount necessary can be determined experimentally, but is dependent upon a host of parameters. This section concludes that the considerations for determining the amount are well known in the art and described in standard textbooks.

From the art and standard textbooks it can be learned that pipamperone is used as a sedative neurolepticum at a dose of 40 mg/day and higher (see for instance the enclosed instructions of the manufacturer).

Obviously, the treatment regimen will start with a dose as extensively tested and recommended by the manufacturer. Thus, the instructions of the manufacturer will provide a further guiding principle for the dose used (cf. instructions of the manufacturer). Only after several weeks of observation, the MD can evaluate whether the prescribed dose is effective or not. In case the medicine appears not to be effective, it is to be expected that either the dose will be ***increased*** or a ***different medicine*** will be prescribed!

Indeed, the instruction manual from the manufacturer advises to increase the starting dose to the maximum tolerable dose. The teaching is always ***unidirectional***, *i.e.* to increase a dose. There is no incentive to treat an anxiety disorder with a low dose.

There is no teaching of lowering a dose. Hence, routine experimentation would be increasing a dose, and observing whether an effect is realized. If no effect is observed, the person skilled in the art will turn to another medicine.

Moreover, in the present invention, the enhanced clinical effect is dependent upon two compounds. However, at other doses, these compounds have no mutual effect, or even have opposing effects. Indisputably, this adds to the complexity of determining any dose.

Thus, applicant maintains that determining at which dose pipamperone augments the efficacy of a second compound is certainly not routine, but either goes against the

teaching in the art or amounts to an undue burden.

Applicant maintains that the present invention is not obvious over Dudley et al. for at least the following:

(i) In diagnosing an anxiety disorder, the person skilled in the art would be motivated to use testosterone in view of Dudley et al., but not combining specifically testosterone with citalopram and pipamperone, considering that only testosterone is used when classic antidepressants ***do not work***;

(ii) Finding the combination of citalopram with pipamperone amounts to an undue burden, in view of the huge amount of possibilities provided in Dudley et al.;

(iii) The person skilled in the art would not be motivated to specifically combine citalopram and pipamperone (in conjunction with testosterone), since neither citalopram nor pipamperone is a preferred compound;

(iv) Finding the appropriate dose of pipamperone, at which pipamperone has a synergistic effect on citalopram amounts to an undue burden, considering that no dose preference is given in Dudley et al., that the prior art teaches to use the highest dose possible; and that the simultaneous effects of three compounds (including testosterone) must be considered; and

(v) Not all elements are present, *i.e.* a starting dose of pipamperone.

Accordingly, applicant maintains that the present invention is not obvious in view of Dudley et al.

Dodman

The Examiner asserts that Dodman (US 5,762,960) teaches that pipamperone serves to alleviate the anxious state of mind and reduce mental anxiety (cf. col.10, lines 20-21).

Applicant notes that Dodman relates to a veterinary method for clinically

modifying the behavior of ***dogs*** exhibiting ***canine affective aggression*** using preferential/discriminatory serotonin reuptake inhibitors. In this regard, Dodman relates to dog models only. Accordingly, Dodman is not applicable to the present invention for treatment of human patients. In this regard, Dodman states on col.10, lines 24-26, that "[t]hese combination therapies are ***strictly limited***, however, to the anxious state of mind and the treatment of "anxiety" in the ***domesticated animal***" (emphasis added). See also, Summary of the Invention in column 11 of Dodman.

Applicant also notes that pipamperone in combination therapy is only discussed in the "Background of the Invention", setting out the problems which are apparently solved by Dodman. The use of combination therapies in general, thus including pipamperone, is discouraged (cf. col.10, from line 27 onwards). In other words, based on the teaching of Dodman, the person skilled in the art would never be motivated to use an SSRI with pipamperone.

Applicant further notes that Dodman mentions pipamperone on only three occasions. In particular, in col.9, lines 37-39 and col.10, lines 24-26, pipamperone in combination with clomipramine is described. It is applicant's understanding that clomipramine may be considered a tricyclic compound, but not an SSRI. Although in the cited two instances this combination is used for treating an anxious state of mind (in dogs), Dodman stresses the use of pipamperone as a neuroleptic (*i.e.* antipsychoticum). Column 9, lines 56-59 is the third occasion in which pipamperone is described, but for treating ***aggressive behaviour***, which is not an anxiety disorder.

In addition, Dodman does not teach the dose of pipamperone required by the present set of claims.

Considering the disclosure by Dodman as a whole, it will be obvious that Dodman

(i) teaches away from using combination therapy;

(ii) teaches away from using pipamperone;

(iii) is limited exclusively to dogs; and

(iv) does not teach any applicability for humans.

Sanchez

The Examiner asserts that Sanchez (US 2002/0086899) teaches the use of escitalopram (the S-(+)-enantiomer of citalopram) in the treatment of anxiety disorder (e.g. Abstract).

Applicant notes that Sanchez relates solely to the use of escitalopram. Indeed, paragraph 0007 discloses that escitalopram provides potent effects. However, Sanchez is utterly silent on combination therapies, let alone with pipamperone, and even less with pipamperone at the claimed dose.

Conclusions

Applicant maintains that none of the cited references teach or suggest the presently claimed invention for reasons set out above.

It is further submitted that the person skilled in the art has no motivation to combine these three documents. Specifically, Dodman relates exclusively to canines, discourages combination therapies and discourages the use of pipamperone. Hence, the person skilled in the art would never combine Dodman with Dudley et al., which relates to humans. In addition, there is no incentive to combine Dudley et al. with Sanchez, since Sanchez relates exclusively to escitalopram and its effects, but is completely silent on combination therapies, let alone synergy, while Dudley et al. does not mention escitalopram at all.

Finally even if the teachings of these documents are combined, then there appear insurmountable gaps in the combined teachings. Specifically, there is no specific teaching to use pipamperone with an SSRI. There is no guidance whatsoever on the dose of

pipamperone. In fact, the instructions by the manufacturer are the only guidance in this regard, but these instructions teach away from the claimed dose. There is no teaching that pipamperone would have an effect on an SSRI, even less that the effect of the SSRI can be increased by this low dose of pipamperone. There is no guidance that a combination therapy would work in the absence of testosterone.

Applicant maintains that the cited references do not teach or suggest the claimed invention. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Status of U.S. Patent Family Members

Applicant would also like to advise the Examiner of the status of co-pending patent family members.

1. U.S. Patent Application No. 10/725,965. The claims have been subject to a restriction requirement. An Office Action on the merits of the application was issued on January 23, 2008.

2. U.S. Patent Application No. 10/803,793. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on May 3, 2007 and on October 19, 2007.

3. U.S. Patent Application No. 10/984,683. The claims have been subject to a restriction requirement. An Office Action on the merits of the application issued on August 10, 2007.

4. U.S. Patent Application No. 10/580,962. An examination report has not yet issued in connection with this application.

CONCLUSIONS

In view of the amendments and remarks made herein, reconsideration and withdrawal of the rejections set forth in the October 2, 2007 Office Action are respectfully requested. If there are any minor matters preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

A check for $60.00 is enclosed for the fee for a one month extension of time for a small entity. No additional fee is deemed necessary in connection with the submission of this reply. However, if any other fee is required with this reply or to maintain the pendency of the subject application, authorization is hereby given to withdraw the amount of any such fee from Deposit Account No. 01-1785. Overpayments may also be credited to Deposit Account No. 01-1785.

Respectfully submitted,

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Dated: February 4, 2008
New York, New York

By _____
Alan D. Miller, Reg. No. 42,889

[logo] JANSSEN-CILAG B.V. EVALUATION BOARD] [stamp: MEDICINES

1. NAME OF THE MEDICINAL PRODUCT

Dipiperon tablets 40 mg.
Dipiperon drops 40 mg/ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dipiperon tablets contain pipamperone dihydrochloride corresponding to 40 mg pipamperone per tablet. Dipiperon drops contain pipamperone dihydrochloride corresponding to 40 mg pipamperone per ml (20 drops per ml; 2 mg per drop).

3. PHARMACEUTICAL FORM

Tablets and drops.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Psychoses.
Symptomatic treatment of serious forms of agitation and anxiety.

4.2 Posology and method of administration

In maintenance treatments an attempt must always be made to establish the minimum effective dose (through regular adjustments to the dose). In general the guidelines are as follows:

Adults
- initial dose: 40 to 80 mg a day, divided in two doses, over 1 to 2 weeks. The optimal anti-psychotic dose is reached after 3 to 6 weeks. If necessary the dose may be increased to a maximum of 360 mg per day
- maintenance dose (over numerous months): to be established individually, depending on the result obtained and the level in which it is tolerated.

Children:
- initial dose: 20 mg per day, divided over two doses. The optimal therapeutic dose varies from 20 to 40 mg.
- maintenance dose (over numerous months): to be established individually depending on the results obtained and the extent by which the medicine is tolerated.

To allow individual adjustment, starting with 20 mg per day is recommended and to increase that dose by 20 mg to between 40 and 120 mg per day.
The final dose is preferably given about one hour before bed.

Note
For the elderly starting with half the initial dose is recommended and increasing this gradually. The blood pressure must then be checked regularly.

4.3 Contraindications

- Depression of the central nervous system
- Comatose conditions
- Hypersensitivity to Dipiperon, or other butyrophenones.

- Cardiovascular insufficiency (due to the possible hypotensive effect of Dipiperon).
- Neurological disorders with extrapyramidal symptoms.

4.4 Special warnings and precautions for use

– A few cases of sudden inexplicable death in psychiatric patients treated with antipsychotics, including Dipiperon. Due to the nature of the incident it was not possible to establish the role Dipiperon played in this.
– There have been rare reports of QT-extension and serious ventricular arrhythmias, including torsade de pointes (TDP) in the use of pipamperone. Care must be taken when administering if there is cause present for QT-interval extension, e.g.: congenital extension of the QT-interval, hypokaliemia or hypomagnesemia, bradycardia, heart rhythm disorders and simultaneous treatment with medicines that extend the QT-interval, such as class Ia antiarrhythmics (e.g. kinidine) and class III (e.g. amiodarone).
– Dipiperon must be administered with the necessary care to patients with cardiovascular disease due to the possible occurrence of hypotension in patients with endogenous depression.
– Older patients may be more sensitive, especially for extrapyramidal effects.
– Patients suffering from epilepsy require careful attention because antipsychotics may lower the stimulus threshold. If necessary the dose of anti-convulsion therapy must be adjusted for these patients.
– Tardive dyskinesia may occur in long term treatment with antipsychotics (especially at high doses). These symptoms may worsen temporarily or even appear after the cessation of the treatment. The risk of irreversibility is greater in older patients and patients with organic brain damage. Patients should be examined for this periodically from 3-6 months after therapy starts and must also be informed in advance of this risk.
– Dosing must be done with care in cases with Parkinson's disease and spastic paralysis.
– Depression in the narrowest sense can become visible as a result of antipsychotics. A mood may arise as a result of taking antipsychotics that is difficult to distinguish from depressive symptoms.
– Account must be taken in patients with psycho-organic disorders of the greater risk of side effects.
– Dosing must be done with care in patients with liver function disorders because pipamperone is metabolised in the liver.
– As with other antipsychotics, one must be aware with Dipiperon of the appearance of so-called malignant neuroleptic syndrome, in which the main are: hyperthermia, extreme muscle rigidity and autonomous instability. In addition the following may arise: an increase of the serum creatinine phosphokinase level and leukocytosis, tachypnoea, changes of consciousness and profuse sweating. Rabdomyolysis and the corresponding kidney impairment are usually life threatening. Anticholinergics and benzodiazepines are often given first except for general supportive measures (external cooling and rehydration). In serious cases these drugs are insufficiently effective and dantrolene and/or dopamine-agonists must be given. If this therapy is not effective or in an extreme life-threatening situation electro-convulsion therapy may save lives.

4.5 Interactions with other medicinal products and other forms of interaction

– There are rare reports of QT-extension and serious ventricular arrhythmias, including torsade de pointes in the use of pipamperone. The simultaneous use of

medicines that extend the QT-interval, such as class Ia antiarrhythmics (e.g. kinidine) and class III (e.g. amiodaron) must be avoided.

- Dipiperon potentiates hypnotics and analgesics, so that they can be given at a lower dose. Patients that use alcohol, barbiturates or other opiates or narcotic analgesics should consequently be treated with circumspection.
- Dipiperon can potentiate sedation caused by benzodiazepines and antihistamines.
- Simultaneous use of antihypertensives increases the risk of hypotension.
- The simultaneous use of other antipsychotics, lithium, antidepressants, anti-Parkinson medicines and drugs with a central anticholinergic effect increases the risk of the occurrence of tardive dyskinesia.
- It may be expected that antipsychotics block the function of dopamine-agonists, such as bromocriptine, lisuride and levodopa.

– Antacids reduce the oral absorption of antipsychotics.
– The anti-α1-adrenerge function of pipamperone may strengthen the blood pressure reducing effect of fenoxybenzamine, labetalol and other α-blocker sympatholytics, as well as of methyldopa, reserpine and other central antihypertensives. On the other hand the blood pressure reducing effect of guanethidine is blocked.
– Agents that induce an increase of the hepatic enzyme activity (barbiturates, phenytoine and carbamazepine), accelerate the breakdown of antipsychotics. A combination of a number of anti-psychotics (e.g. loxapine) with diuretics, like furosemide and chloorthiazide, may greatly increase the excretion of water, sodium and sometimes also chloride.

4.6 Pregnancy and lactation

Pregnancy
There is insufficient data available concerning the use of Dipiperon in human pregnancy to assess the possible risk. As yet there have been no indications of harm in animal tests.
If it is necessary to use Dipiperon during pregnancy, the risks must be carefully weighed against the therapeutic benefits.

Breastfeeding
No data is available concerning the excretion of pipamperone in breast milk. The benefits of breastfeeding must be weighed against the possible risks to the child.

4.7 Effects on ability to drive and use machines
The ability to respond when participating in traffic or operating dangerous machines may be influenced negatively by antipsychotics.

4.8 Undesirable effects
Extrapyramidal reactions with Dipiperon are dose related and vary from patient to patient. The following extrapyramidal reactions may occur:
– dose dependent Parkinson-type symptoms (hypokinetic or hypokinetic-rigidity syndrome);
– acute dyskinetic-dystone symptoms;
– dose dependent akathisia.

In addition other random motor symptoms arise. After long-term use (after months to years) movement disorders (in particular tardive dyskinesia) may appear both during and after treatment (see also sections Special warnings and precautions for use and Interactions).
The following side effects may also occur: convulsions, worsening of depressions and dysphoria and malignant neuroleptic syndrome (see special warnings and precautions for use).
Other reports concerning the central nervous system
There have been reports of: depression, fatigue, insomnia, headaches, dizziness, grand mal-convulsions.
Gastro-intestinal symptoms
Nausea, vomiting and lack of appetite have been reported.

Endocrine side effects
– Antipsychotics generally cause a dose dependent increase in prolactin (see also Warnings and precautions for use). This increase may result in galactorrhoea, cycle disorders in women and gynaecomasty and impotence in men who did not previously have any sexual dysfunction.
– Erectile and ejaculation dysfunction may occur in men (e.g. priapism and retrograde ejaculation).
– An occasional report has been made of hyponatremia.

Cardiovascular side effects
Occasionally benign tachycardia and hypotension occur. There have been very rare reports of QT-extension and/or ventricular arythmias, including torsade de pointes. A few cases of Asystole have been reported.

Other rare side effects
– Mild, and usually passing, decreases in blood cell counts.
– Liver function deviations or cholestatic hepatitis.
– Hypersensitivity reactions like rash.
– A few cases of a Stevens-Johnson-like syndrome have been reported.
– Blurred vision, urine retention, urine incontinence, oedema and disorders to the body temperature.

4.9 Overdose

In the event of overdose it may be expected that the side effects that appear with a normal dose will be more obvious. A few cases have been described in which a daily dose of 1280 mg was tolerated well. The main side effects in these patients were extrapyramidal side effects and mild hypotension and/or sedation. There have been a few very rare reports of QT-extension, ventricular arrhythmias, including torsade de pointes and/or cardiac arrest. Account should be taken of the risk of heart arrhythmias possibly connected to QT-extension. In the event of overdose admission to an intensive care department is essential.
There is no specific antidote for Dipiperon. For that reason supportive measures must be taken. One should also consider that multiple drugs may be involved in the case of an overdose.
With an acute overdose the airways must be kept free and ensure that the patient is given sufficient oxygenation and ventilation. Gastric lavage should be carried out

(after intubation, if the patient has lost consciousness) and activated carbon and an osmotic functioning laxative (sodium sulphate) administered. The cardiovascular parameters must also be monitored immediately. Possible arrhythmias can be detected via ECG-monitoring. The ECG should also be monitored considering the risk of QT-extension. Hypotension and a collapse of the blood circulation should be treated with the methods used for this, such as intravenous administration of fluids and/or sympathicomimetics.
Anticholinergic medication must be administered in the case of serious extrapyramidal effects. The patient must be carefully observed and monitored until full recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pipamperone is a neuroleptic from the butyrophenone group. It combines 5-HT2-antagonism with a less pronounced blocking of α1-adrenoreceptors and D2-dopaminoreceptors. Pipamperone has no anticholinergic effects.

5.2 Pharmacokinetic properties

In elderly volunteers maximum levels were reached approximately 2 hours after an oral administration; the elimination half-life observed varies between 11 and 35 hours. Biotransformation of pipamperone primarily occurs as a result of the reduction of the keto-function, hydroxylation of piperidine, deamine oxidase and N-oxidation. It is primarily eliminated as metabolites through the kidneys. Whether the metabolites contribute to the effect is unknown. There is no information available concerning the plasma protein-binding of pipamperone. Passage through the blood-brain barrier has been observed in rats.

5.3 Preclinical safety data

Nil of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets: lactose, corn starch, saccharose, Talc, Magnesium Stearate.

 Ned.

Deze bijsluiter bevat belangrijke informatie. Lees hem zorgvuldig en in zijn geheel door voordat u dit geneesmiddel gaat gebruiken.
Heeft u nog vragen of wilt u meer informatie of advies, raadpleeg dan uw arts of apotheker.
Laat anderen nooit uw geneesmiddelen gebruiken. Gebruik zelf ook geen middelen van anderen.
Gooi deze bijsluiter niet weg; het kan nodig zijn om hem nogmaals door te lezen.

TRADEMARK

Dipiperon *tabletten 40 mg*

Dit geneesmiddel wordt in de handel gebracht door:

JANSSEN-CILAG B.V.

Wat zijn Dipiperon-tabletten?
Dipiperon-tabletten zijn witte, ronde tabletten. De ene kant heeft twee breuklijntjes. Aan de andere kant staat: Janssen. Elke tablet bevat 40 mg pipamperon. Dat is de stof die zorgt voor de werking van Dipiperon. Pipamperon is werkzaam tegen psychosen. Dat zijn bepaalde stoornissen in de hersenen. Ook wordt Dipiperon gebruikt bij de behandeling van ernstige vormen van onrust en opwinding.
De tabletten bevatten verder: lactose, maïszetmeel, saccharose, talk en magnesiumstearaat.
Dipiperon-tabletten zitten in verpakkingen met 20 tabletten. Er is ook een flacon met 1000 tabletten verkrijgbaar en er bestaat een speciale ziekenhuisverpakking met 50 afzonderlijk verpakte tabletten.
Dipiperon tabletten 40 mg zijn in het Register van Geneesmiddelen ingeschreven onder RVG 00183 op naam van Janssen-Cilag B.V., Postbus 90240, 5000 LT Tilburg, telefoon: 0800-242 42 42.

Wanneer gebruikt u Dipiperon-tabletten?
U heeft Dipiperon gekregen omdat u lijdt aan een psychose. Dat is een stoornis in het functioneren van de hersenen die te maken heeft met denken, voelen en/of doen, zoals verwardheid, hallucinaties, een gestoorde waarneming (zoals het horen van de stem van iemand die er niet is) en achterdochtigheid, vervreemding van de maatschappij en uitzonderlijk in zichzelf gekeerd zijn, maar ook de stemmingsstoornissen, de angst en de spanning die er het gevolg van zijn.
Het is ook mogelijk dat u Dipiperon krijgt omdat u erg onrustig of opgewonden bent.

Wanneer mag u Dipiperon niet gebruiken?
Gebruik Dipiperon-tabletten niet wanneer u weet dat u overgevoelig bent voor een van de bestanddelen in de tabletten. Welke dit zijn, vindt u onder: "Wat zijn Dipiperon-tabletten?". Gebruik Dipiperon ook niet wanneer u overgevoelig bent voor soortgelijke geneesmiddelen tegen psychosen. Overgevoeligheid kunt u herkennen aan bijvoorbeeld huiduitslag. Als u hiervan last krijgt, stop dan met Dipiperon en raadpleeg uw arts.
Gebruik Dipiperon-tabletten ook niet wanneer u suf of traag bent als gevolg van uw aandoening of door alcohol- of medicijngebruik.
Dipiperon kan een bloeddrukverlagend effect hebben, daarom mag u het niet gebruiken als u een onvoldoende hartwerking heeft.
Gebruik Dipiperon ook niet als u lijdt aan neurologische aandoeningen die gepaard gaan met bewegingsstoornissen, zoals trillen, geringe spierstijfheid en rusteloosheid in de benen.
Bij coma mag Dipiperon ook niet worden gebruikt.
Raadpleeg bij twijfel altijd uw arts.

Welke speciale voorzorgen moet u nemen?
- Zwangerschap
Er is nog weinig over bekend of Dipiperon bij zwangerschap schadelijk is. Uit proeven met dieren is tot nu

toe geen schadelijkheid gebleken.
Bent u in verwachting of gedurende de periode van de behandeling van plan in verwachting te raken? Overleg dan eerst met uw arts of u Dipiperon kunt innemen.

- Borstvoeding
Het is niet bekend of de werkzame stof in Dipiperon in de moedermelk terechtkomt. Overleg daarom met uw arts of de voordelen van borstvoeding opwegen tegen de mogelijke risico's voor het kind.

- Ouderen
Ouderen moeten meestal minder Dipiperon innemen dan er wordt voorgeschreven voor andere volwassenen (zie "Hoeveel Dipiperon moet u innemen?"). Ouderen kunnen gevoeliger zijn voor de bijwerkingen van Dipiperon, vooral voor bewegingsstoornissen.

- Kinderen
Kinderen krijgen een lagere dosering dan volwassenen voorgeschreven, afhankelijk van de leeftijd (zie "Hoeveel Dipiperon moet u innemen?").

- Hart- en vaatziekten, verminderd functioneren van de lever, depressies, epilepsie
Vertel het uw arts wanneer u lijdt aan een van deze aandoeningen. Nauwkeurig medisch toezicht zou noodzakelijk kunnen zijn wanneer u Dipiperon gebruikt. Bovendien moet de dosering misschien worden bijgesteld.

- Deelname aan het verkeer, bedienen van machines en dergelijke
Dipiperon kan uw waakzaamheid of rijvaardigheid nadelig beïnvloeden. U dient hiermee rekening te houden bij het besturen van voertuigen of bij het bedienen van gevaarlijke machines.

Andere geneesmiddelen, alcohol en Dipiperon
Stel uw arts of apotheker altijd op de hoogte wanneer u ook andere geneesmiddelen gebruikt of binnenkort gaat gebruiken. Sommige geneesmiddelen mogen namelijk niet tegelijk worden gebruikt en soms vereist gelijktijdig gebruik bepaalde aanpassingen (van bijvoorbeeld de dosering).
Tijdens de behandeling met Dipiperon mag u niet beginnen met andere medicijnen zonder dat u hiervoor uw arts of apotheker raadpleegt.

- Zo kan Dipiperon het effect versterken van alcohol en geneesmiddelen die het reactievermogen verminderen (bijvoorbeeld slaapmiddelen, kalmerende middelen, verdovende pijnstillers, bepaalde middelen tegen allergische aandoeningen, bepaalde middelen tegen depressieve stemming). Drink daarom geen alcohol en neem de genoemde middelen alleen wanneer uw arts ze voorschrijft.
- Stel uw arts zeker op de hoogte wanneer u geneesmiddelen gebruikt voor behandeling van de ziekte van Parkinson. Sommige van deze middelen werken Dipiperon tegen. Bovendien is dan de kans groter dat er bepaalde bijwerkingen ontstaan: vreemde bewegingen van de tong, het gezicht, de mond of de kaken.
- Vertel het uw arts ook altijd als u begint of stopt met geneesmiddelen die carbamazepine of fenytoïne bevatten. Dit zijn bepaalde geneesmiddelen tegen epilepsie of tegen ernstige pijnaanvallen in het gezicht. Hetzelfde geldt als u geneesmiddelen gebruikt die stoffen bevatten waarvan de naam eindigt op "barbital". Deze middelen worden ook gebruikt bij epilepsie of tegen slaapstoornissen.
- Licht uw arts ook in wanneer u geneesmiddelen gebruikt tegen verhoogde bloeddruk. Dipiperon kan het effect van deze middelen veranderen.
- Overleg ook met uw arts of apotheker als u middelen gebruikt die maagzuur binden. Dipiperon zou dan minder goed kunnen werken.

Waarschuwingen
Dipiperon zou vreemde bewegingen (van de tong, het gezicht, de mond of de kaken) kunnen veroorzaken. Raadpleeg uw arts wanneer dit gebeurt.
Dipiperon zou ook hoge koorts, versnelde ademhaling, transpireren, stijve spieren, verwardheid en verminderd bewustzijn teweeg kunnen brengen. In dit geval dient u onmiddellijk uw arts te raadplegen.

Hoe moet u Dipiperon innemen?
U moet Dipiperon tweemaal per dag innemen: 's ochtends en 's avonds voor het slapengaan. U kunt het bij de maaltijd of tussen de maaltijden door innemen. Doe dit met een paar slokken water of een andere drinkbare vloeistof (echter geen alcoholische drank!).

Hoeveel Dipiperon moet u innemen?

Het is zeer belangrijk dat u de juiste hoeveelheid Dipiperon inneemt; deze zal van persoon tot persoon verschillen. Daarom zal uw arts de dosering bijstellen totdat het gewenste effect wordt verkregen. Volg de aanwijzingen van uw arts dus zorgvuldig op en verander of stop de dosering niet zonder uw arts te raadplegen!
De dosering is gewoonlijk als volgt.
- Volwassenen en jongeren ouder dan 15 jaar
Start de behandeling met 2x per dag ½-1 tablet (40-80 mg per dag). Na 1 tot 2 weken zal uw arts bekijken hoe u op de behandeling reageert. Afhankelijk hiervan zal de dosis worden bijgesteld tot het resultaat optimaal is. Meestal is dit na 3 tot 6 weken.
Belangrijke opmerking: neem nooit meer dan 2x per dag 4½ tablet (360 mg per dag).
- Ouderen
Het is het beste de helft te nemen van de dosis die beschreven is voor andere volwassenen. Uw arts of apotheker zal u vertellen hoeveel dit in uw situatie is.
- Kinderen
Start de behandeling met 2x per dag ¼ tablet (20 mg per dag). Afhankelijk van het resultaat past de arts de dosis aan. De beste resultaten ziet men bij ½-1 tablet per dag (20-40 mg).
- Langdurige behandeling
Bij een langdurige behandeling is de dosis afhankelijk van het resultaat en hoe u het middel verdraagt.

Wat moet u doen bij overdosering?
Raadpleeg onmiddellijk een arts wanneer u of iemand in uw omgeving te veel Dipiperon heeft ingenomen. Zeker wanneer een of meer van de volgende verschijnselen optreden: verminderd bewustzijn, sufheid, slaperigheid, snelle of onregelmatige hartslag, hartstilstand, ernstig trillen of ernstige spierstijfheid. Daarnaast mag u geactiveerde kool (verkrijgbaar in de apotheek) innemen. Geactiveerde kool neemt de Dipiperon op die nog in de maag aanwezig is en die nog niet door het lichaam is opgenomen.

Mogelijke bijwerkingen
- Moeheid, slaperigheid of duizeligheid kunnen voorkomen.
- Bewegingsstoornissen zoals trillen, geringe spierstijfheid en niet stil kunnen zitten, kunnen voorkomen. Raadpleeg uw arts in dit geval. Misschien verlaagt hij de dosis waarna deze verschijnselen verdwijnen.
- Bij langdurig gebruik (maanden tot jaren) kunnen vreemde bewegingen (van de tong, het gezicht, de mond of de kaken) voorkomen. Raadpleeg uw arts wanneer dit gebeurt.
- Wanneer u behandeld wordt voor epilepsie, kan het zijn dat er toch een aanval optreedt.
- Na langdurig gebruik kunnen vrouwen last krijgen van wat melkafscheiding uit de tepels en menstruatiestoornissen, terwijl er bij mannen in sommige gevallen in zeer lichte mate borstontwikkeling kan plaatsvinden. Impotentie of erectiestoornissen kunnen optreden.
- Hoofdpijn, depressie, slapeloosheid, misselijkheid, braken, verminderde eetlust, verlaagde bloeddruk of snelle pols kunnen voorkomen, maar zijn zeldzaam.
- Wazig zien, moeite met plassen, incontinentie (het niet kunnen ophouden van urine), gezwollen enkels of een duidelijke verandering in lichaamstemperatuur kunnen een enkele keer voorkomen.
- Leverproblemen, een ernstige huidaandoening of hartproblemen kunnen voorkomen, maar zijn zeer zeldzaam. Neem contact op met uw arts als deze verschijnselen bij u optreden..
- Overgevoeligheid voor Dipiperon komt zelden voor. Overgevoeligheid kunt u herkennen aan bijvoorbeeld huiduitslag. Als u hiervan last krijgt, stop dan met Dipiperon en raadpleeg uw arts.

Belangrijk
In zeer zeldzame gevallen kan Dipiperon ook hoge koorts, versnelde ademhaling, transpireren, stijve spieren, verwardheid en verminderd bewustzijn teweegbrengen. In deze gevallen dient u onmiddellijk uw arts te raadplegen.

Aarzel niet alle hinderlijke, onverwachte of niet te verklaren verschijnselen te melden aan uw arts of apotheker.

Hoe bewaart u Dipiperon-tabletten?

Bewaar Dipiperon-tabletten steeds in de verpakking die u van de apotheek kreeg, met deze gebruiksaanwijzing erbij. U kunt de informatie dan nog eens nalezen. De juiste bewaarwijze is: beneden 30 °C en buiten het bereik van kinderen.

Hoe lang zijn Dipiperon-tabletten houdbaar?
Dipiperon-tabletten zijn houdbaar tot de datum op de verpakking (mits op de juiste manier bewaard). Voorbeeld: *niet te gebruiken na 08 - 2003* of *EXP.: 08 - 2003* betekent dat u het geneesmiddel na augustus 2003 niet meer mag gebruiken.
Raadpleeg bij twijfel uw apotheker.

Deze gebruiksaanwijzing is samengesteld in november 2000.

Wat u over geneesmiddelen in het algemeen moet weten...

Vertel het uw arts of apotheker altijd als u ook andere geneesmiddelen gebruikt of gaat gebruiken. Sommige geneesmiddelen mogen namelijk niet tegelijk worden gebruikt. Dit geldt ook voor geneesmiddelen die u zonder recept koopt.

Voordat patiënten een geneesmiddel krijgen, is het eerst uitgebreid onderzocht. Als u geneesmiddelen op de juiste wijze gebruikt, is de kans klein dat er iets mis gaat.
Wat houdt een juist gebruik in?
- *Gebruik het middel alleen voor het doel waarvoor u het heeft gekregen.*
- *Gebruik het alleen in de voorgeschreven hoeveelheid.*
- *Gebruik het niet langer dan is aangegeven.*

Houd alle geneesmiddelen buiten het bereik van kinderen.

Laat anderen nooit uw geneesmiddelen gebruiken. Gebruik zelf ook geen middelen van anderen.

Raadpleeg onmiddellijk een arts of de eerstehulpafdeling van een ziekenhuis als iemand een overdosis van een geneesmiddel heeft ingenomen.

Bewaar alle geneesmiddelen in de verpakking die u van de apotheek kreeg, met de gebruiksaanwijzing erbij. U kunt de informatie dan nog eens nalezen.

Bewaar geneesmiddelen op een droge plaats, dus bijvoorbeeld niet in de badkamer; die is meestal te vochtig.

Breng overgebleven en oude geneesmiddelen terug naar de apotheek of stop ze in de chemobox: uit veiligheid en voor bescherming van het milieu.

dipiptb/mia/00/11/28